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REVIEW

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Oxidative Stress and Inflammation in Cardiovascular Diseases and Cancer: Role of Non-coding RNAs

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High oxidative stress, Th1/Th17 immune response, M1 macrophage inflammation, and cell death are associated with cardiovascular diseases. Controlled oxidative stress, Th2/Treg anti-tumor immune response, M2 macrophage inflammation, and survival are associated with cancer. MiR-21 protects against cardiovascular diseases but may induce tumor growth by retaining the anti-inflammatory M2 macrophage and Treg phenotypes and inhibiting apoptosis. Down-regulation of let-7, miR-1, miR-9, miR-16, miR-20a, miR-22a, miR-23a, miR-24a, miR-26a, miR-29, miR-30a, miR-34a, miR-124, miR-128, miR-130a, miR-133, miR-140, miR-143-145, miR-150, miR-153, miR-181a, miR-378, and miR-383 may aid cancer cells to escape from stresses. Upregulation of miR-146 and miR-223 may reduce anti-tumor immune response together with miR-21 that also protects against apoptosis. MiR-155 and silencing of let-7e, miR-125, and miR-126 increase anti-tumor immune response. MiR expression depends on oxidative stress, cytokines, MYC, and TGF-β, and expression of silencing lncRNAs and circ-RNAs. However, one lncRNA or circ-RNA may have opposite effects by targeting several miRs. For example, PVT1 induces apoptosis by targeting miR-16a and miR-30a but inhibits apoptosis by silencing miR-17. In addition, levels of a non-coding RNA in a cell type depend not only on expression in that cell type but also on an exchange of microvesicles between cell types and tumors. Although we got more insight into the function of a growing number of individual non-coding RNAs, overall, we do not know enough how several of them interact in functional networks and how their expression changes at different stages of disease progression.

INTRODUCTION

Mitochondrial reactive oxygen (ROS), immune response, inflammation, and apoptosis are associated with cardiovascular diseases and cancer [1-7]. Non-coding RNAs regulate these stress conditions [8-10]. They compass small non-coding RNAs or microRNAs or miRs, circular (circ-) RNAs, and long non-coding (lnc)RNAs [11-14]. We recently gave an overview of the relationship between non-coding RNAs, which are deregulated in association with metabolic diseases, and are related to cardiovascular diseases and cancer [15]. Here, we review non-coding RNAs related to cardiovascular diseases and cancer without taking into account a prior relationship with metabolic diseases, focusing on stress conditions mentioned above. Interestingly, we identified a cluster of miRs related to high oxidative stress, Th1/Th17 immune response, M1 macrophage inflammation, and apoptosis in cardiovascular diseases. Importantly, differential expression of this cluster in tumors allowed cancer cells to

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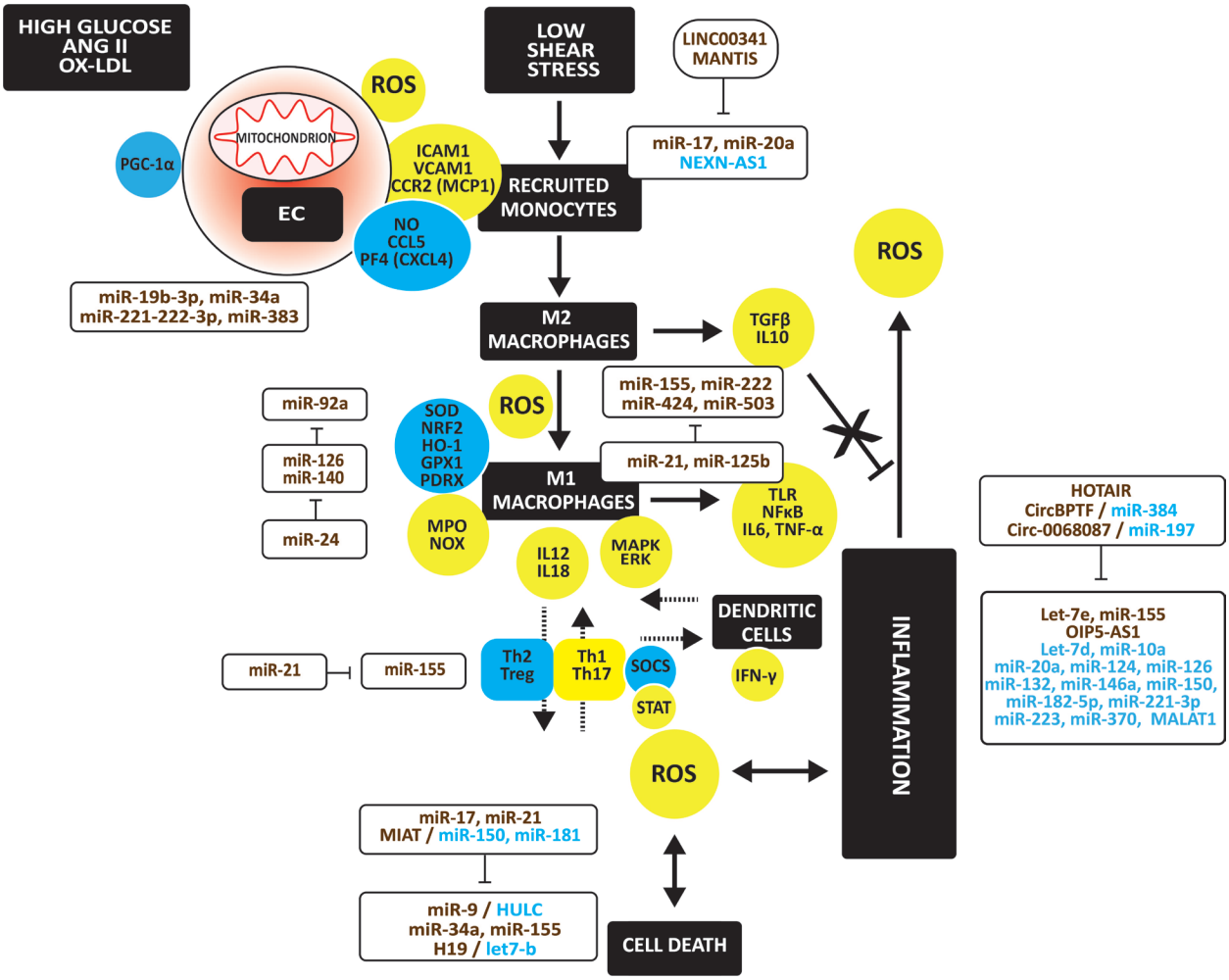

Figure 1. **Oxidative stress, immune response, inflammation, and apoptosis in atherosclerosis**. High glucose, ANGII, ox-LDL, and shear stress cause endothelial dysfunction with mitochondrial oxidative stress, releasing ROS. Thus, oxidative stress is due to a shift to more oxidative and less antioxidative factors. Injured endothelium induces adhesion and infiltration of monocytes which differentiate to macrophages. ROS induce M2 to M1 macrophage polarization. In addition, M1 macrophages release proinflammatory cytokines, which induce ROS release and apoptosis in vascular cells. Furthermore, a shift from Th2 and Treg cells to Th1 and Th7 cells occurs, all associated with the activation of DCs. Upregulated regulators are in yellow circles, downregulated ones in blue circles. Upregulated non-coding RNAs are in brown, down-regulated ones in blue.

escape from oxidative stress, anti-tumor immunity and inflammation, and apoptosis. Their expression depends on oxidative stress, cytokines, MYC, and TGF-β. Differences in miR expressions may be due to differential expression of mainly silencing lncRNAs and circ-RNAs. In addition, we show that many of these lncRNAs and circ-RNAs target several miRs, causing even opposite effects on stress conditions.

OXIDATIVE STRESS AND INFLAMMATION WITHIN ATHEROSCLEROSIS

Figure 1 illustrates the mechanisms in atherosclerosis and the involvement of non-coding RNAs in regulating oxidative stress, inflammation, and apoptosis in atherosclerosis. Exposure of endothelial cells (ECs) to high glucose, angiotensinogen (ANG II), oxidized LDL (ox-LDL), and shear stress causes endothelium dysfunction. Dysfunction is due to impaired non-canonical Wnt and phosphatidylinositol 3-kinase (PI3K) / Akt serine/threonine kinase 1 (Akt) / nitric oxide synthase (NOS) signaling [16-18]. Endothelial stress causes adhesion and infiltration of monocytes via vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and the C-C motif chemokine receptor 2 (CCR2; or MCP-1 receptor). The downregulation of Krüpel-like factor (KLF)-2 and KLF4 induces these adhesion molecules [19]. The binding of monocytes cells to

ECs involves C-C motif chemokine ligand 5 (CCL5) and platelet factor-4 (PF4 or CXCL4) [20].

Usually, infiltrated monocytes differentiate into anti-inflammatory M2 macrophages. They secrete transforming growth factor (TGF)-β and IL10, which counteract vascular inflammation and immune cell activation. However, injured endothelium releases high amounts of ROS, polarizing M2 towards inflammatory M1 macrophages. This polarization involves the activation of toll-like receptors (TLRs) and downstream NFκB and the release of inflammatory cytokines, such as interleukin (IL)-6 and TNF-α [21]. In addition, activated macrophages secrete myeloperoxidase (MPO) and NADPH oxidase (NOX), oxidizing LDL. The disruption of antioxidant defense systems consisting of superoxide dismutases (SODs) [22,23], NRF2 - heme oxygenase (HO)-1 [24], glutathione peroxidase-1 (GPX1) [25], and peroxiredoxin 1 (PRDX1) and PRDX2 [26,27] augment oxidative stress.

The activation of monocytes/macrophages in the vessel wall initiates the innate immune response [28]. Th1 cells exceed the number of Th2 cells in atherosclerotic plaques. Dendritic cells (DCs), activated by cytokines released by M1 macrophages, induce secretion of interferon (IFN)-γ by Th1 cells, no longer counteracted by IL4 produced by Th2 cells. The number of Treg cells producing IL4, IL5, IL10, and IL13, is also lower. Activated DCs release IFN-γ that induces M2 to M1 polarization and secretion of inflammatory cytokines, inducing apoptosis of vascular cells, associated with ROS release.

NON-CODING RNAS REGULATING OXIDATIVE STRESS AND INFLAMMATION WITHIN ATHEROSCLEROSIS

Oxidative Stress

MiR-19b-3p, miR-221-3p, and miR-222-3p repress the proliferator-activated receptor gamma coactivator (PGC)-1α protein expression leading to mitochondrial oxidative stress [29]. MiR-34a and miR-383 mitochondrial biogenesis increase oxidative stress by repressing sirtuin (SIRT)-1, preventing deacetylation of PGC-1α [30,31].

Advanced glycation end products (AGEs) and ox-LDL induce miR-92a, silencing HO-1 [32]. In contrast, miR-126 induces SIRT1 and SOD2 expression, protecting ECs against ROS production and senescence [33]. MiR-140-5p decreased oxidative stress and ROS levels by increasing the protein expression of NRF2 and SIRT2, and HO1 [34]. However, miR-24 may hamper this NRF2 activation [35] (Figure 1).

Inflammation

MiR-17a and miR-20a induce hypoxia-induced infiltration of monocytes and activation of M1 macrophages [36]. In addition, repression of nexilin F-actin binding protein antisense RNA 1 (NEXN-AS1) increases NFκB, monocyte-specific adhesion molecules, and inflammatory cytokines [37]. In contrast, lncRNA LINC00341 and MANTIS repress adhesion molecules [38,39], the latter by targeting KLF2 and KLF4.

MiR-155, miR-222, miR-424, and miR-503 induce M1 macrophage polarization [40]. In contrast, miR-21 and miR-125b retain macrophages in the M2 phenotype [41,42].

Ox-LDL significantly upregulates let-7e that activates NFκB and inflammation. The long intergenic non-protein coding RNA 1826 (LINC01826 or Lnc-MKI67IP-3) may sponge let-7e, suppressing its proinflammatory effects [43]. Ox-LDL-induced miR-155 and the lncRNA Opa-interacting protein five antisense RNA 1 (OIP5-AS1) accelerate ox-LDL-induced EC injury and inflammation via the TLR4/NFκB signaling pathway [44,45]. Furthermore, the silencing of let-7d by lin-28 homolog (LIN28)-b and the decrease of miR-10a, miR-20a, miR-124, miR-126, miR-132, miR-146a, miR-150, miR-182-5p, miR-221-3p, miR-223, and miR-370, and the metastasis-associated lung adenocarcinoma transcript 1 (MALAT) induce inflammation [46-55]. In contrast, lncRNA HOX transcript antisense RNA (lncRNA HOTAIR), the bromodomain PHD finger transcription circular RNA (CircBPTF; or hsa_circ_0000799) targeting miR-384 [56], and the circRNA circ_0068087 silencing miR-197 protect against inflammation [56-58].

MiR-21 promotes Treg differentiation [59]. In contrast, miR-155 increased Th17 cells and decreased Th2 and Treg cells [60,61] (Figure 1).

Apoptosis

High miR-9, due to low hepatocellular carcinoma upregulated long non-coding RNA (HULC) [62], miR-34a [63], and miR-155 [64] induce apoptosis. H19 increases apoptosis by silencing let-7b [65]. In contrast, miR-17, miR-21, and MIAT sponging miR-150 and miR-181 protect against apoptosis [66-69] (Figure 1).

OXIDATIVE STRESS AND INFLAMMATION WITHIN CARDIOMYOPATHY

Figure 2 illustrates the mechanisms and the involvement of non-coding RNAs in regulating oxidative stress, inflammation, and apoptosis in the development of cardiomyopathy. Endothelial dysfunction is a hallmark of cardiomyopathy. As in atherosclerotic plaques, mitochondrial dysfunction, due to impaired SIRT1 /

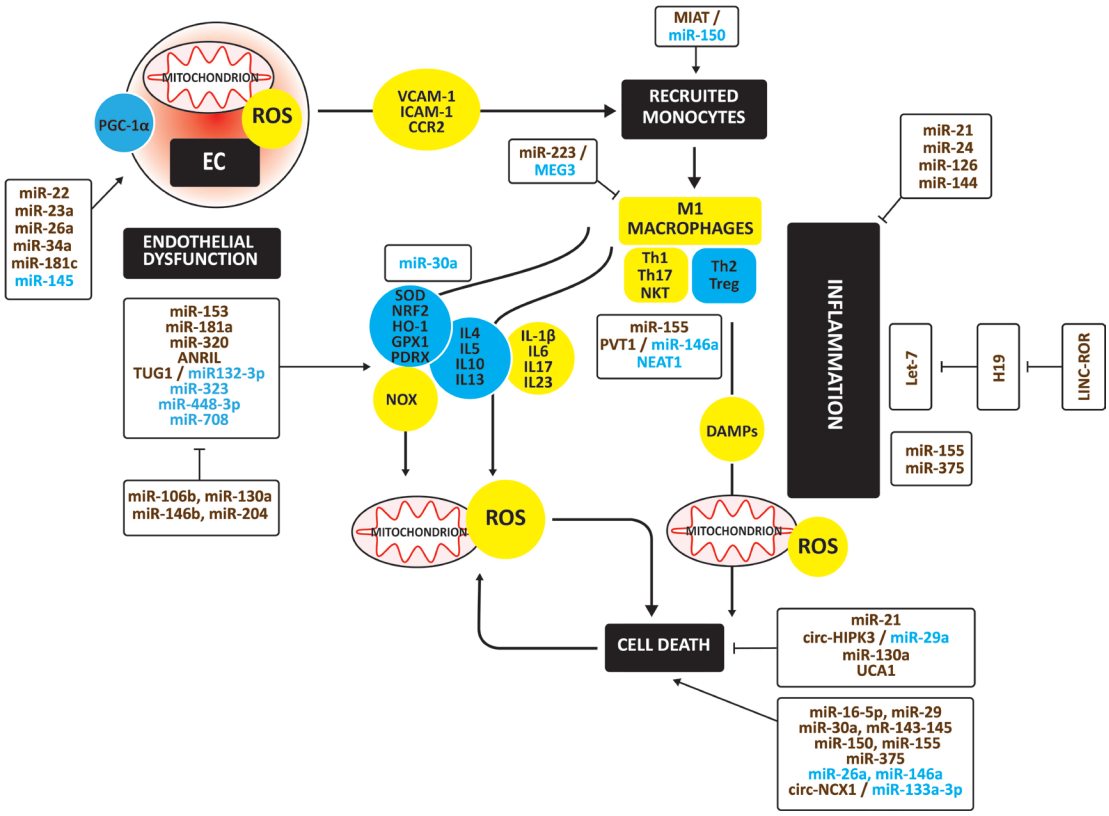

Figure 2. **Oxidative stress, immune response, inflammation, and apoptosis in cardiomyopathy**. Endothelial dysfunction is a hallmark of cardiomyopathy. As in atherosclerotic plaques, mitochondrial dysfunction induces ROS to release. Thus, oxidative stress is due to a shift to more oxidative and less antioxidative factors. Again, the initial inflammatory response associated with increased oxidative stress consists of the infiltration of monocytes which differentiate to M1 macrophages secreting inflammatory cytokines. This inflammatory response also augments damage-associated molecular patterns (DAMPs), which trigger inflammation and mitochondrial ROS, inducing cell death. During the later phase of the immune response, T lymphocytes infiltrate. Cardiac T cells undergo a phenotypic change. Th2 and Treg cells decrease whereas Th1 and Th17 cells increase. This shift increases inflammatory cytokines and ROS, inducing cardiac apoptosis. Upregulated regulators are in yellow circles, downregulated ones in blue circles. Upregulated non-coding RNAs are in brown, down-regulated ones in blue.

PGC-1αsignaling, induces ROS to release. The mitochondrial respiratory chain and oxidases of the NOX family are significant sources of ROS in cardiomyocytes [70]. In addition, low SODs [71], GPX [72], and PRDX [73] and impaired PGC-1α/HO-1 [74] and Keap1-NRF2 signaling [75] increases oxidative stress.

Again, the initial inflammatory response associated with increased oxidative stress consists of the infiltration of monocytes involving VCAM-1, ICAM1, and CCR2 [76]. The infiltrated monocytes differentiate to M1 macrophages secreting inflammatory cytokines. This inflammatory response also augments damage-associated molecular patterns (DAMPs) [77-81], which trigger inflammation and mitochondrial ROS, inducing cell death [82].

During the later phase of the immune response, T lymphocytes infiltrate. Cardiac T cells undergo a phenotypic change to induce cardiac injury and remodeling [83]. Th1 and Th17 cells increase, while Th2 and Treg cells decrease. This shift increases inflammatory IL-1β, IL6, IL17, IL23, and decreases anti-inflammatory IL4, IL5, IL10, and IL13 [84-87]. Inflammation is associated with cardiac fibrosis and cardiac apoptosis, typically prevented by Treg cells, which are decreased [88].

NON-CODING RNAS REGULATING OXIDATIVE STRESS AND INFLAMMATION WITHIN CARDIOMYOPATHY

Oxidative Stress

MiR-22, miR-23a, miR-26a, and miR-34a increase mitochondrial ROS and cell death, the latter by targeting SIRT1 / PGC-1α [89-92]. MiR-181c disturbed the mitochondrial complex IV increasing ROS production [93].

Down-regulation of miR-145 is associated with mitochondrial dysfunction due to lower SIRT1 [94] (Figure 2).

MiR-153 [95] and miR-320 [96], silencing NRF2, and miR-181a [97], silencing GPX1, increased ROS production, disrupted the mitochondrial structure, and activated the mitochondrial apoptotic pathway. The CDKN2B antisense RNA 1 (ANRIL) and downregulation of miR-448-3p increases NOX expression and ROS level [98,99]. The decrease of miR-323-3p and miR-708 is associated with decreased SOD [100,101]. In the oxidative stress-challenged heart, TUG1 sponges miR-132-3p, epigenetically inhibiting antioxidative PRDX2 and heat shock protein Hsp70 [102].

In contrast, miR-106b, miR-130a, miR-148b, and miR-204 may decrease oxidative stress and improve heart function [103,104] (Figure 2).

Inflammation

Silencing miR-150 by myocardial infarction-associated transcript (MIAT) may increase monocytes' infiltration [105]. ANG II decreases miR-30a inducing ICAM-1 and VCAM by ECs [106]. Down-regulation of maternally expressed three lncRNA (MEG3) decreased M1 and increased M2 macrophage polarization by upregulating miR-223 [107].

MiR-155 induces Th17 cells [108]. PVT1 was associated with higher autophagy in Treg cells by targeting miR-146a [109]. Conversely, deletion of NEAT1 reduces Treg cells [110].

Let-7 induces inflammation. H19 represses let-7, but miR-146a and long intergenic non-protein coding RNA, a regulator of reprogramming (LINC-ROR), compete out this repression [111,112]. MiR-155 and miR-375 induce inflammation and apoptosis [113,114]. In contrast, miR-21 [115], miR-24 [116], miR-126 [117], and miR-144 [118] protect against inflammation [115-118] (Figure 2).

Apoptosis

MiR-16-5p [119], miR-29a [120], miR-30a-5p [121], miR-143-145 [122], miR-150 [123], and miR-155 [124] increase apoptosis. Down-regulation of miR-26a and mi-146a is associated with increased apoptosis [125,126]. In addition, ROS increases the circular RNA derived from solute carrier family eight-member A1 (SLC8A1 or NCX1; CircNCX1) that promotes cardiomyocyte apoptosis by acting as an endogenous miR-133a-3p sponge [127].

In contrast, miR-21 [128], the hypoxia-induced exosomal homeodomain interacting protein kinase three circular RNA (circHIPK3), sponging miR-29a [129], and miR-130a [104] inhibit apoptosis. Urothelial cancer-associated one lncRNA (UCA1) protected from mitochondrial and endoplasmatic reticulum oxidative stress [130] (Figure 2).

OVERVIEW OF NON-CODING RNAS RELATED TO OXIDATIVE STRESS AND INFLAMMATION WITHIN CARDIOVASCULAR DISEASES ALSO RELATED TO CANCER

Oxidative Stress

Notably, ROS is increased in cancer cells. However, there is a strict balance of ROS levels in the growing tumor to allow cancer cell proliferation and avoid tumor cell apoptosis. NRF2 regulates the cellular redox status in cancer cells. Besides inducing antioxidant and detoxification genes, NRF2 induces metabolic reprogramming during stress. Increased fumarate inactivates Keap1 and activates NRF2. NRF2 induces antioxidant response genes; for example, *HO-1* is essential for retaining colony-forming capacity [131]. In addition, GPX1 is a gatekeeper restraining the oncogenic power of mitochondrial ROS generated by SOD2 [132]. PRDX family is essential in regulating oxidative stress avoiding apoptosis in cancer cells [133,134] (Figure 3).

Compared to cardiovascular tissues, silencing of miR-22a, miR-23a, miR-24a, miR-29, miR-34a, miR-140, miR-153, miR-181, and miR-383 reduces oxidative stress by de-repressing NRF2, increasing HO-1, SOD, and PDRX [135-146]. Table 1 summarizes candidate silencing lncRNAs and circ-RNAs.

Inflammation and Anti-Tumor Immunity

Hypoxia, one of the hallmarks of cancer, is caused by an insufficient oxygen supply due to a deficient tumor microcirculation. Hypoxia by activating Wnt/β-catenin reduces the anti-cancer immune responses by (a) reducing survival, the cytolytic and migratory activity of effector cells such as $CD4^+$ cells, $CD8^+$ cytotoxic T cells, natural killer-like T cells, and natural killer (NK) cells, (b) reducing the production and release of effector cytokines, (c) supporting immunosuppressive Treg cells, myeloid-derived suppressor cells and M2 macrophages, (d) increasing the production and release of immunosuppressive cytokines, and (e) inducing the expression of immune checkpoint inhibitors [147]. Wnt ligands stimulate tumor-associated macrophages to produce IL-1β, thus driving systemic inflammation [148]. TAMs are mainly alternatively activated M2 macrophages with immunosuppressive and tumor-promoting capabilities. Hypoxic environment and hypoxia-treated glioma cell supernatants can polarize macrophages toward an M2 phenotype through TGF-β [148,149]. TNF-α derived from M2 tumor-associated macrophages promotes EMT

Table 1. Potential Silencing lncRNAs and Circular RNAs

MiR	LncRNA	Circular RNA
Let-7e	NEAT1 [237], SNHG4 [238]	
MiR-9	CASC2 [239], HULC [240], KCNQ1OT1 [241], NEAT1 [242], TUG1 [243]	FOXO3 [244], MTO1 (hsa_circRNA_0007874, or hsa_circRNA_104135) [245]
MiR-16a		PVT1 [246,247]
MiR-17a	MIR17HG [248], BLACAT1 [249], HNF1A-AS1 [250], HOTAIR [251], H19 [252], lincRNAp21 [253], MALAT1 [254], NEAT1 [255], NR2F1-AS1 [256], XIST [257]	ITCH [258], LONP2 [259], MTO1 [260], cSMARCA5 (hsa_circ_0001445) [261], PVT1 [262]
MiR-20a	HNF1A-AS1 [263], HOTAIR [264], SNHG16 [265]	PVT1 [266]
MiR-22	MIR22HG [267], HOTAIR [268], H19 [269], LINC00968 [270], MALAT1 [271], MEG3 [272], MIAT [273], NCK1-AS1 [274], PART1 [275]	ITCH [276]
MiR-23a	GAS5 [277], MALAT1 [278], MEG3 [279], NEAT1 [280], SNHG5 and SNHG7 [281,282], XIST [283], ZEB1-AS1 [284]	
MiR-24	CASC2 [285], CCAT1 [286], HOXA11-AS [287], NEAT1 [288], SOX21-AS1 [289]	
MiR-26a	DLGAP1-AS1 [290], GAN1 [291], GAS5 [292], HCG11 [293], MALAT1 [294], MEG3 [295], MINCR [296], NEAT1 [297], NORAD [298], OIP5-AS1 [299], SNHG5 and SNHG6 [300,301], TUG1 [302], ZNF561-AS1 [303]	Circ-0001146 (derived from miR-26a) [304]
MiR-29	DANCR, GAS5, and SNHG5 [305], H19 [306], MEG3 [307]	
MiR-30a	LEF1-AS1 [308,309], NORAD [309]	PVT1 [310]
MiR-34a	ARSR [311], CCAT1 [312], FEZF1-AS1 [313], GAS5 [314], HNF1A-AS1 [315], HOTAIR [316], KCNQ1OT1 [317], LINC-ROR [318], MACC1-AS [319], MALAT1 [320], MIAT [321], NEAT1 [322], OIP5-AS1 [323], TUG1 [324], XIST [325]	ANRIL [326], MYLK [327]
MiR-128	MIR4435-2HG [328], HULC [329], MEG3 [330], MIAT [331], OIP5AS1 [332], SNHG3 [333], SNHG16 [334], SNHG22 [335], TUG1 [336], ZNF561-AS1 [303]	PVT1 [337]
MiR-140	CCAT1 [338], H19 [339], MALAT1 [340], MIAT [341], NR2F1-AS1 [342], OIP5-AS1 [343], SNHG16 [344], TUG1 [345]	PVT1 [346]
MiR-143	MIR143HG [347], BLACAT1 [348], CCAT1 [349], HOTAIR [350], H19 [351], MALAT1 [352], NCK1-AS1 [353], OIP5-AS1 [354], SNHG1 [355], SOX2-OT [356], TMPO-AS1 [357], TUG1 [358], UCA1[359], ZEB2-AS1 [360]	FOXM1 [361], FOXO3 [362], PVT1 [363]
MiR-150	BLACAT1 [364], FOXD3-AS1 [365], HULC [366], MIAT [68], NEAT1 [367], PART1 [368], SNHG10 [369], ZFAS1 [370]	PVT1 [371]
MiR-153	FGD5-AS1 [372], HIF1A-AS2 [373], KCNQ1OT1 [374], NEAT1 [375], OIP5-AS1 [376], TTN-AS1 [377], TUG1 [378], XIST [379]	CircPCNXL2 [380]
MiR-155	MIR155HG [381], CCAT1 [382], HOXA11-AS [383], MEG3 [384], MIAT [385], NORAD [386], UCA1 [387], XIST [388]	Circ-CHST15 [389]
MiR-181	CCAT1 [390], MEG3 [391], SNHG6 [183], SNHG7 [392]	
MiR-222	MIR222HG [393], CASC2 [394], DANCR [395], GAS5 [396]	
MiR-383	HOXC13-AS [397], TMPO-AS1 [398]	
MiR-424	MYLK-AS1 [399]	
MiR-615		Circ-ZNF609 [400]

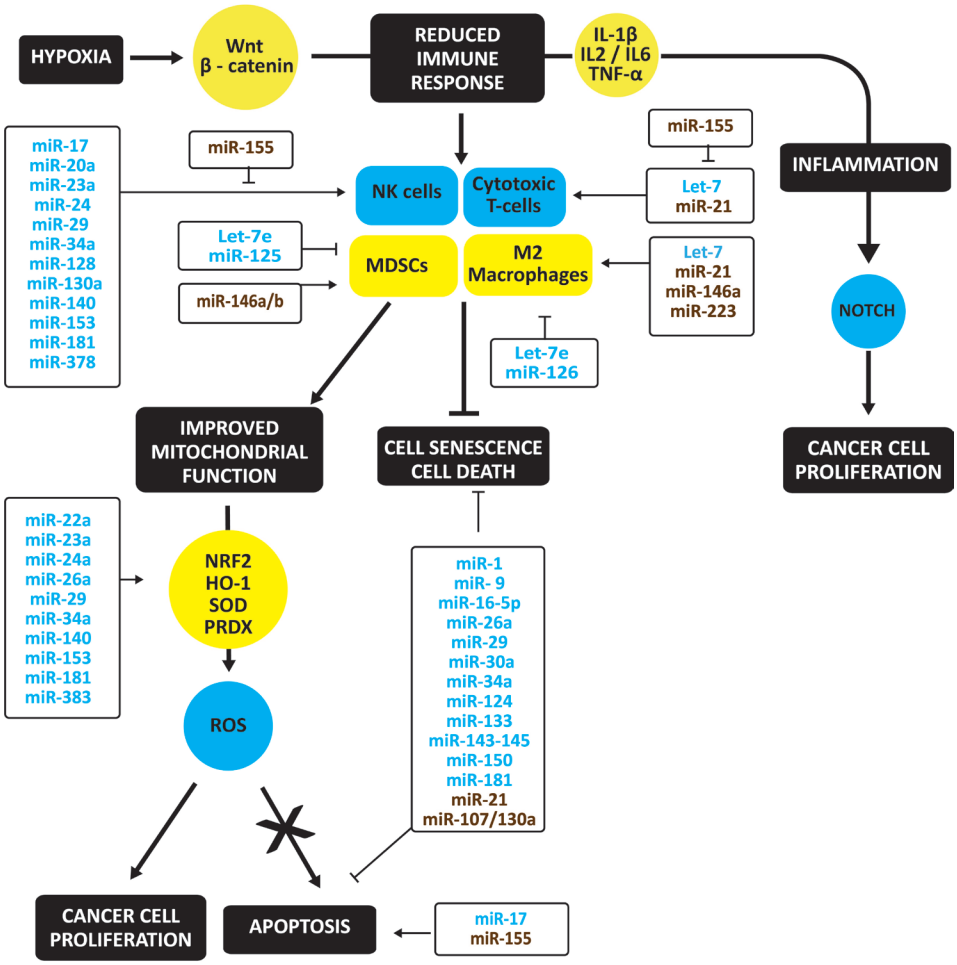

Figure 3. **Oxidative stress, immune response, inflammation, and apoptosis in cancer**. Hypoxia, one of the hallmarks of cancer, reduces the anti-cancer immune responses by activating Wnt/β-catenin. As a result, cytotoxic T cells and NK cells decrease, and immunosuppressive Th2 and Treg cells, myeloid-derived suppressor cells and M2 macrophages increase. This shift augments immunosuppressive cytokines and decreases inflammatory cytokines. Notably, ROS is increased in cancer cells. However, there is a strict balance of ROS levels in the growing tumor to allow cancer cell proliferation and avoid tumor cell apoptosis. This protection is due to a shift from oxidative to antioxidative factors. Upregulated regulators are in yellow circles, downregulated ones in blue circles. Upregulated non-coding RNAs are in brown, down-regulated ones in blue.

and cancer stemness through the Wnt/β-catenin pathway. Reprogramming TAMs towards classically activated M1 macrophages may thwart tumor-associated immunosuppression and unleash anti-tumor immunity [150].

Suppression of let-7 increased M2 macrophages and abated recruitment of activated cytotoxic T lymphocytes [151]. MiR-21, miR-146a-5p, and miR-223 may promote M2-polarization, but the down-regulation of let-7e and miR-126 increases M1 macrophages [152-158]. MiR-21 decreases, whereas miR-155 stimulates cytotoxic T cells [159-161]. MiR-146a and miR-146b may induce differentiation of monocytes to MDSCs, suppressing the anti-tumor immune response, whereas down-regulation of let-7e and miR-125 increases this response [162].

Effective $CD8^+$ T cells appear to target predominantly tumor-specific neoantigens. To elicit an effective antitumor response, these antigens have to be taken up by dendritic cells (DCs) and cross-presented for $CD8^+$ T cell priming. Then, the antigen must be directly presented for recognition by primed $CD8^+$ T cells and killing [163]. MiR-155 may $CD8^+$ T cell fitness and improve the anti-tumor activity of adoptively transferred low-affinity tumor-infiltrating lymphocytes, in particular, by rendering them more resistant to the glucose-deprived environment of solid tumors [164].

Downregulation of miR-17 [165], miR-20a [166], miR-23a [167], miR-24 [168], miR-29 [169], miR-34a [170], miR-128 [171], miR-130a [172], miR-140-3p [173], miR-153 [174], miR-181 [175], and miR-378 [176] may suppress NK cytotoxicity. MiR-155 activates

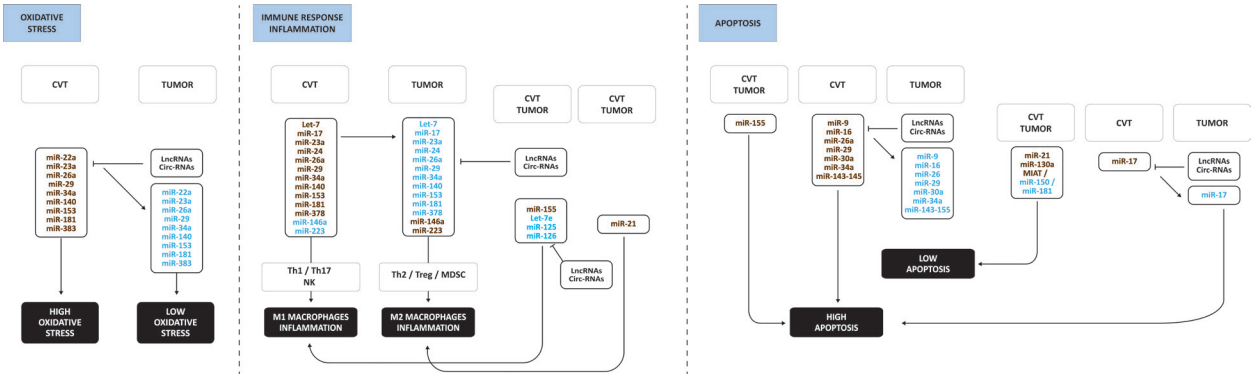

Figure 4. **Main differences in miR expression in tumors compared to cardiovascular tissues**. These changes in miR expression support the shift from high oxidative stress to low oxidative stress, from Th1/Th2 to Th2/Treg with more activated MDSC and less activated NK cells, and from M1 macrophage to M2 macrophage inflammation, ultimately leading to less apoptosis in tumors. The downregulation of miRs is possibly due to the overexpression of lncRNAs and circ-RNAs summarized in Table 1. Upregulated non-coding RNAs are in brown, down-regulated ones in blue.

NK cells [177].

Apoptosis

Down-regulation of miR-9, miR-16-5p, miR-26a, miR-29, miR-30a, miR-34a, miR-124, miR-133, miR-143-145, miR-150, and miR-181a/b protect tumor cells against apoptosis, whereas upregulation of miR-155 induce apoptosis [178-191]. Specifically, miR-19-3p and miR-200c sensitize cancer cells to apoptosis induced by CD95 (or FAS) [192-194]. However, they are often reduced in tumor cells. The decrease of miR-206, miR-1-3p, and miR-133b upregulates the Fas Apoptotic Inhibitory Molecule (FAIM), which counteracts oxidative stress-induced loss of cell viability [195,196]. As in cardiovascular tissues, high miR-21 [197] and miR-107/miR-130a impede apoptosis in tumors [198]. MiR-21 enriched in exosomes from M2 polarized TAMS can be directly transferred from macrophages to cancer cells to protect them against apoptosis [199]. In contrast, silencing of miR-17 [200] induces apoptosis (Figure 3). Table 1 summarizes potential silencing lncRNAs and circular RNAs.

AGEs stimulate oxidative stress generation through the interaction with a receptor for AGE (RAGE), while oxidative stress promotes AGE's formation and increases RAGE expression. This crosstalk between the AGE-RAGE system and oxidative stress generation may form a positive feedback loop, thus further increasing the risk for cancers, particularly in patients with diabetes [201,202]. The high-mobility group box 1 protein (HMGB1), a late inflammatory cytokine that signals danger to the immune system through RAGE and TLR, induces the expression of miR-221 and miR-222, associated with higher malignancy scores [203]. MiR-185-5p binds to RAGE, reversing the EMT and migration and invasion of cancer [204,205]. Furthermore, blockage of RAGE with an anti-RAGE antibody suppressed induction of miR-21 [206].

Figure 4 illustrates the main differences in miR expression in tumors compared to cardiovascular tissues explaining the shift from high oxidative stress to low oxidative stress, from Th1/Th2 to Th2/Treg with less activated NK cells, and from M1 macrophage to M2 macrophage inflammation. The downregulation of miRs is possibly due to the overexpression of lncRNAs and circ-RNAs summarized in Table 1.

DISCUSSION

This review focused on miRs related to oxidative stress, immune response related to T cell and MDSC differentiation, inflammation related to M2 or M1 macrophages, and apoptosis. In addition, we identified a cluster of miRs involved in the pathogenesis of cardiometabolic diseases and cancer. This cluster contains: members of let-7 family, miR-1, miR-9, miR-16, miR-17, miR-20a, miR-21, miR-22a, miR-23a, miR-24a, miR-26a, miR-29, miR-30a, miR-34a, miR-128, miR-130a, miR-140, miR-143-145, miR-146a, miR-150, miR-153, miR-155, miR-181 family, miR-221-222, miR-223, miR-378, and miR-383.

MiR-21 protects against cardiovascular diseases by retaining the anti-inflammatory M2 macrophage and Treg phenotypes and inhibiting apoptosis. However, the same effects may induce tumor growth. Transfer of exosomal miR-21 from M2 macrophages to cancer cells may even increase protection against apoptosis. Upregulation of miR-146 and miR-223 may reduce anti-tumor immune response by activating MDSCs and retaining the M2

macrophage phenotype. As in cardiovascular tissues, miR-155 levels are high in tumors. MiR-155 and silencing of let-7e, miR-125, and miR-126 increase anti-tumor immune response.

Most other miRs are downregulated in tumors but upregulated in cardiovascular tissues. Inflammation, oxidative stress, MYC oncogene, and TGF-β regulate miR expression. IL6 increases miR-17, but IFN-γ suppresses miR-17, thereby reverting anti-inflammatory and anti-oxidative action in breast tumors [207-209]. CXCL12 / CXCR4 up-regulate XIST that silences miR-133a-3p, protecting against apoptosis [210]. Mitochondrially encoded COX2 induces methylation of the promoter of let-7, down-regulating let-7 and up-regulating SOX2 [211]. The expression of non-coding RNAs in tumors depends on MYC. MYC induces miR-155 [212] but may silence other miRs by upregulating ANRIL [213], H19, [214-216], and PVT1, enhancing cancer cells' proliferation. However, PVT1 may induce or inhibit MYC expression [217-220]. MYC directly down-regulates let-7a, let-*7d*, and let-7g [221], miR-29 [222-226], and miR-34a 4a indirectly by inducing lncRNA-SNHG7 [227,228]. TGF- β reduces miR-29a [229] and miR-34a, thereby up-regulating VEGF and retaining the M2 macrophage phenotype [230,231] or miR-124 [232]. TGF-β1 also decreases miR-133a/b, protecting against apoptosis [233].

These opposite changes in miR expression profiles may be due to differential expression of lncRNAs and circ-RNAs, as discussed above for ANRIL and PVT1. Table 1 shows that other miRs are prone to silencing by lncRNA and circ-RNAs. The same lncRNA and circ-RNAs may obtain the same effect by targeting several miRs. For example, MALAT1 and NEAT1 may reduce oxidative stress and anti-tumor response by targeting miR-23a, miR-24a, miR-26a, and miR-34a. MALAT1 also protects by targeting miR-22 and miR-140, NEAT1 by targeting miR-150 and miR-153.

On the other hand, they may obtain a similar effect by targeting a different miR. For example, NEAT1 may protect against apoptosis by targeting miR-9, MALAT1 by targeting miR-143. In addition, the effects of TUG1 overlap partially with these of MALAT1 and NEAT1 by targeting miR-9, miR-26a, miR-34a, miR-128, miR-140, miR-143, and miR-153. However, the same non-coding RNA may have opposite effects by targeting several miRs. For example, PVT1 may protect against apoptosis by targeting miR-16a and miR-30a but induce apoptosis by targeting miR-17. This non-specificity in targets and function obscures their mechanistic and clinical value. This lack of knowledge is cumbersome because papers identifying a new non-coding RNA are published each month claiming a new function.

Previously, we showed that most of the identified are regulated by adipokines, glucose, insulin, blood pressure, inflammatory cytokines, and ox-LDL related to metabolic diseases, like obesity, type 2 diabetes, and non-alcoholic fatty liver disease. These metabolic diseases increase the overall risk for cardiovascular diseases and cancer [15]. Thus, the identified cluster of miRs will most probably not be specific markers of cardiovascular diseases or cancer. They may, however, be essential to understanding disease mechanisms.

In addition, we have to be aware that levels of non-coding RNAs in a cell type are not only determined by the expression in that cell type but also by exosome-mediated exchange of non-coding RNAs between cell types in a tissue or between tissues [9,15,234,235].

Unfortunately, information about the sequence of changes in expression profiles of non-coding RNAs at different stages of disease progression is lacking. We do not even know which non-coding RNAs are expressed together at the same stages. Indeed, we lack algorithms to determine if non-coding RNAs have any clinical value in addition to phenotypic, therapeutic, behavioral, and social data in a predicting model. Artificial intelligence (AI) or machine-learning methods may be applied to fit vast amounts of expression data combined with phenotypic, therapeutic, behavioral, and social data [236].

Abbreviations: AGEs, advanced glycation end products; Akt, Akt serine/threonine kinase 1; AMPK, AMP-activated protein kinase; ANG, angiotensin; ANRIL, CDKN2B anisense RNA 1; ARSR, DNA-binding transcriptional repressor ArsR; ATP, adenosine triphosphate; BLACAT1, bladder cancerassociated transcript 1; BMP, bone morphogenetic proteins; BPTF, bromodomain PHD finger transcription factor; CASC2, cancer susceptibility 2; CCAT1, colon cancer-associated transcript 1; CCL5, C-C motif chemokine ligand 5; CCL2 (or MCP1), C-C motif chemokine ligand 2; CCR2 (or MCP-1 receptor), C-C motif chemokine receptor 2; CHST15, carbohydrate sulfotransferase 15; circ, circular; CM, cardiomyocyte; DAMP, damage-associated molecular patterns; DANCR, differentiation antagonizing non-protein coding RNA; DC, dendritic cell, DLGAP1, DLG associated protein 1; ECs, endothelial cells; ERK, extracellular-signal-regulated kinase; FEZF1, FEZ family zinc finger 1; FGD5, FYVE, RhoGEF and PH domain containing 5; FOXD3, forkhead box D3; FOXM1, forkhead box M1; FOXO, forkhead box O; GAN1, gigaxonin; GAS5, growth arrest specific 5; GPX, glutathione peroxidase; HCG11, HLA complex group 11; HIF, hypoxia-inducible factor; HIPK3, homeodomain interacting protein kinase 3; HMGB1, high-mobility group box 1 protein; HNF1A, HNF1 homeobox A; HO, heme oxygenase; HOTAIR, homeobox transcript antisense lncRNA; HOXA11, homeobox 11; HULC, hepatocellular carcinoma upregulatedlong non-coding RNA; H19, H19 imprinted maternally expressed transcript; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IL, interleukin; IRS, insulin substrate receptor; ITCH, itchy E3 ubiquitin protein ligase; KCNQ1OT1, KCNQ1 opposite strand/antisense transcript 1; KLF, Krüppel-like factor; LEF1, lymphoid enhancer-binding factor 1; LIN-28, lin-28 homolog; lnc-RNA, long-non-coding RNA; LncRNA-ATB, long non-coding RNA activated by TGF-β; LINC-ROR, long intergenic non-protein coding RNA, regulator of reprogramming; LONP2, lon peptidase 2; MACC1, MACC1MET transcriptional regulator; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MAPK, mitogen-ac-

tivated protein kinase; MDSC, myeloid-derived suppressor cell; MEG3, maternally expressed 3 lncRNA; MIAT, myocardial infarction-associated transcript; MINCR, MYC-induced long non-coding RNA; MIRT1, myocardial infarction associated with transcript 1; MIR22HG, MIR22 host gene; MTO1, mitochondrial translation optimization 1 homologue; MPO, myeloperoxidase; MYLK, myosin light chain kinase; NCK1, noncatalytic region of tyrosine kinase adaptor protein 1; NEAT1, nuclear paraspeckle assembly transcript 1; NEXN-AS1, nexilin F-actin binding protein antisense RNA 1; NFκB, nuclear factor kappa B; NK, natural killer; NLRP3, NLR family pyrin domain containing 3; NORAD, noncoding RNA activated by DNA damage; NOS, nitric oxide synthase; NOX, NADPH oxidase; NRF2, NF-E2-related factor 2; NR2F1, nuclear receptor subfamily 2 group F member 1; OIP5-AS1, Opa-interacting protein five antisense RNA 1; Ox-LDL, oxidized LDL; OXPHOS, oxidative phosphorylation; PART1, prostate androgen regulated transcript 1; PCNXL2, pecanex 2; PF4 (or CXCL4), platelet factor-4; PPARγ, peroxisome proliferator activated receptor gamma; PGC-1α, proliferator-activated receptor gamma coactivator-1α; PI3K, phosphatidylinositol 3-kinase; PlGF, placental growth factor; PRDX, peroxiredoxin; PTEN, phosphatase and tensin homolog; PVT1, Pvt1 oncogene circular RNA; ROS, reactive oxygen species; SIRT, sirtuin; SLC2A4 (or GLUT4), glucose transporter solute carrier family two-member four; SLC8A1 (or NCX1), solute carrier family eight-member A1; SMARCA5, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 5; SNHG, small nucleolar RNA host gene; SOCS, suppressor of cytokine signaling; SOD, Superoxide dismutases; SOX, SRY-box transcription factor; SOX2-OT, SOX2 overlapping transcript; SPRY4-IT1, Sprouty4-Intron 1; STAT, signal transducers and activators of transcription; TF, tissue factor; TGF, transforming growth factor; TLR, toll-like receptor; TMPO, thymopoietin; TNFα, tumor necrosis factor α; Treg, regulatory T cell; TTN, titin; TUG1, taurine upregulated 1; UCA1, urothelial cancer-associated one lnc-RNA; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; XIST, X inactive specific transcript; ZEB, zinc finger E-box binding homeobox; ZNF, zinc finger protein; ZFAS1, ZNFX1 antisense RNA 1.

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